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RESEARCH ARTICLE

WILSON'S DISEASE IN ADULTS A SERIES OF 13 CASES IN THE GASTROENTEROLOGY DEPARTMENT OF THE UNIVERSITY HOSPITAL OF FEZ

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Abstract

Wilson's disease (WD) is a rare genetic disorder with autosomal recessive transmission. It is a copper toxicosis characterized by an accumulation of free copper mainly in the liver, brain and pericorneal. The objective of this work is to study the clinical, biological and morphological parameters of Wilson's disease as well as the evaluation of liver damage and its complications. We conducted a retrospective study in the gastroenterology department at the HASSAN II University Hospital in Fez on 13 patients over a period of 16 years. There were five men and eight women. The average age of discovery of the disease was 15 years and 8 months, with extremes of 5 years and 36 years. Consanguinity was found in seven patients. Ascites was the main reason for consultation encountered in five patients, followed by jaundice in four patients. Neurological involvement such as tremor and dysarthria was found in four patients. Only one patient presented with acute hepatitis with signs of hepatic encephalopathy. The KAYSER FLEISHER ring was found in four patients. Seven patients had liver damage without neurological damage. The ceruloplasmin measured in twelve patients was low in eight. The copper urine measured in all patients was found to be increased in ten of them. Abdominal ultrasound showed chronic liver disease in eleven patients. Eleven patients were treated with D-penicillamine and two patients were treated with zinc acetate. In terms of evolution, ten patients showed good clinical improvement. One patient presented with hemorrhagic decompensation with death. One patient developed hepatocellular carcinoma and one patient was lost to follow-up after a one-year follow-up period. Early diagnosis of Wilson's disease allows for better management, with an improvement in the vital and functional prognosis of patients.

Introduction:-

Wilson's disease (WD) or "hepato-lenticular degeneration" is a genetic disorder with autosomal recessive transmission. It is a copper toxicosis characterized by tissue accumulation of free copper: mainly hepatic, cerebral and peri-corneal. This monogenic disease results from mutations in the ATP7B gene carried by chromosome 13; this

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gene codes for the ATP7B protein which ensures the transport of copper within the hepatocyte. The global clinical prevalence of the disease varies according to ethnicity, from 12 to 25 cases per million inhabitants. In France, an epidemiological study carried out in 2013 found 906 cases of WD, which leads to a prevalence of 1.5 cases per 100,000 inhabitants **[1].** In Morocco, it remains underestimated due to the difficulty of diagnosis. It produces clinical manifestations, including variable combinations of hepatic, neurological, psychiatric, ophthalmologic and other disorders **[2].** WM usually begins with a presymptomatic period, during which the accumulation of copper in the liver causes subclinical hepatitis that progresses to liver cirrhosis and the development of neuropsychiatric symptoms **[3].** If diagnosed early, it is one of the most treatable hereditary diseases. In the absence of any treatment, the spontaneous evolution is most often fatal. Screening for the disease is essential in the patient's siblings in order to look for asymptomatic forms that are more amenable to treatment. The aim of this work is to contribute to the study of this condition: By studying the clinical, biological and morphological parameters of WM; By assessing liver damage and its complications as well as the evolution of patients after copper chelation treatment and by raising the problems of management of this rare pathology in our context.

Patients and Methods:-

We conducted a descriptive retrospective study, involving 13 patients followed by the gastroenterology department of the Hassan II-Fez University Hospital over a period of 16 years (2004-2020). Thus, all patients over 16 years of age diagnosed or followed for WM in the gastroenterology department of the Hassan II-Fez University Hospital and having a complete file were included. The clinical and paraclinical data of the patients were collected using a pre-established operating sheet from the patients' medical records, hospitalization and adult hepatology consultation registers of the gastroenterology department. The descriptive analysis of the study data was done by calculating the percentages for the qualitative variables, the means and standard deviations for the quantitative variables using an Excel 2019 table.

Results:-

Thirteen cases of WM were diagnosed and followed up in the gastroenterology department of the Fez University Hospital during the study period (2004-2020). The average age of discovery of the disease was 15 years and 8 months, with extremes of 5 years and 36 years. In nine patients, or 69.3% of cases, the diagnosis was made between 10 and 20 years, in 15.3% between 0 and 10 years and in 15.3% at an age greater than 20 years. There was a female predominance, with 8 women (61.6%) against 5 men (38.4%), i.e. a sex ratio of 0.6. The notion of consanguinity was found in 7 patients (53.8%): all had first-degree consanguinity. No consanguinity was found in 6 patients (46.2%). Three cases, or 23% of cases, reported the notion of death in the family (siblings and cousins) at a young age in a picture of probably chronic liver disease. Ascites was the main reason for consultation encountered in 5 patients, followed by jaundice in 4 patients. Neurological involvement such as tremor and dysarthria was found in 4 patients. Only one patient presented in the context of a picture of acute hepatitis with signs of hepatic encephalopathy. Three patients had no functional or physical signs, or 23% were asymptomatic discovered during family screening survey.

The ophthalmological examination revealed the presence of the KAYSER FLEISHER ring in 4 patients (30%). All of whom had associated neurological involvement. Seven patients had liver involvement without neurological involvement. No patient presented signs of cardiac, renal or osteoarticular involvement.

Biologically:

Transaminases were normal in 11 patients (84.6%) and moderately elevated between 2 and 3 times normal in 2 patients (15.4%). The TP was greater than 70% in 9 patients, and between 50% and 70% in 4 patients, no patient had a TP less than 50%.

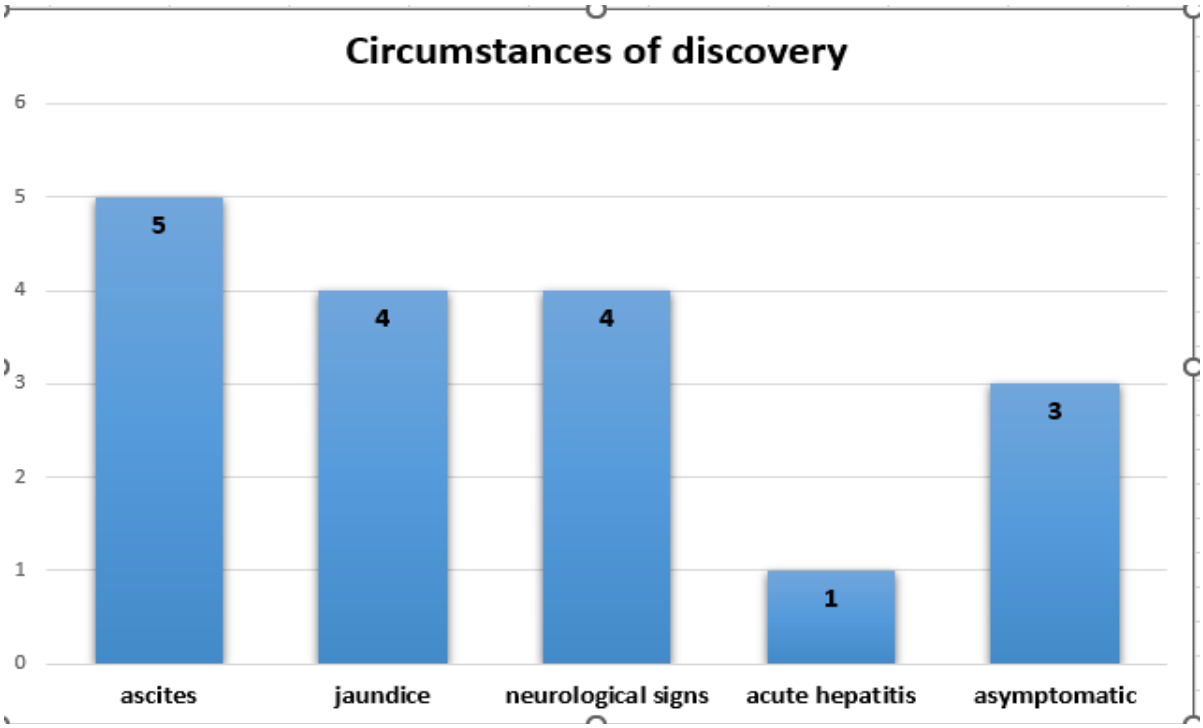
The cholestasis assessment was normal in 12 patients, only 1 patient had a total bilirubin level of 58 mmol/l, a GGT at 3 times normal and a PAL at 3 times normal.

On the hematological level:

The hemoglobin level was normal in 8 patients. Five patients had anemia (normochromic normocytic). Including three cases between 7 and 9 g/dl and two cases between 9 and 10 g/dl. Seven patients in our series had thrombocytopenia, including 4 with moderate thrombocytopenia between 20,000 and 100,000 elements/mm3 and 3

with mild thrombocytopenia between 100,000 and 150,000 elements/mm3. Six patients had leukopenia with a WBC level between 1500 and 4000 elements/mm3.

Copper assessment:
The ceruloplasmin carried out in 12 patients was low < 0.15g/l in 8 cases (66%) and normal in the other 4. The cupremia measured in 9 patients was lowered to <10 µmol/l in 7 cases (77%) and normal in 3 others. The cupruria measured in all patients was found to be increased to >100 microgram/24H in 10 patients (77%). (Table 1)



Copper balance	Low rate (number of patients)	Normal rate (number of patients)	High rate (number of patients)
Ceruloplasmin	**8**	**4**	**0**
Cupremia	**7**	**3**	**0**
Cupruria	**0**	**3**	**10**

Abdominal ultrasound performed in all patients showed chronic liver disease in 11 patients (84%) and normal liver in 2 patients. Dilated portal vein in 8 patients and normal in 4 cases, portal thrombosis in one patient. Presence of splenomegaly in 11 patients, and the presence of ascites in 3 patients. The Child-Pugh Score calculated in 8 patients showed: four patients classified as A5, two patients as A6 and two patients as B7.

Esophagogastroduodenalfibroscopy performed in 12 patients objectified the presence of esophageal varices in 8 patients (66%), of whom 5 had stage III esophageal varices (OV) and 3 patients had stage I OV. 4 patients had normal FOGD.

Brain MRI, performed in 6 patients, objectified central gray nuclei involvement in 3 patients and in the rest of the patients the MRI did not objectify any abnormality.

Liver biopsy, performed in only one patient, the histological result of which is compatible with Wilson's disease.

In terms of treatment, all patients benefited from a dietary consultation with the introduction of a low-copper diet. Eleven patients (84%) were treated with D penicillamine (TROLOVOL®/CUPRIPEN®), including 7 at a dose of 900 mg/day, 3 at a dose of 750 mg/day and 1 patient at a dose of 500 mg/day (maintenance dose) divided into 3

doses. Two patients were treated with Zinc acetate (WILZIN®) at a dose of 150 mg/day at a rate of one 50 mg tablet 3 times a day due to financial problems. Five patients, or 38%, received treatment with zinc sulfate in combination with D-penicillamine to increase the efficacy of the treatment. Six patients (46%) received treatment with Beta-blocker as part of the protocol for preventing upper digestive hemorrhage due to rupture of esophageal varices. Two patients received vitamin B supplementation. Two patients received diuretic treatment for edema-ascitic syndrome. One patient was treated with an antiparkinsonian and a muscle relaxant to alleviate the neurological disorders presented.

In terms of evolution: Ten patients (76%) showed good clinical improvement (digestive and neurological). One patient died after hemorrhagic decompensation. One patient developed hepatocellular carcinoma. One patient was lost to follow-up after one year of follow-up. All patients would benefit from a screening ultrasound scan every 6 months (liver cirrhosis in 11 patients, one patient developed hepatocellular carcinoma put on SORAFENIB after decision of the RCP staff, one patient with normal ultrasound scan).

Discussion:-

Copper is an essential metal required as a cofactor for many metalloproteins. The recommended intake is 0.9 mg/day. Wilson disease (WD) was first described in 1912 by Kinnier Wilson as “progressive lenticular degeneration,” a fatal familial neurological disease accompanied by cirrhosis **[4].** Subsequently, the role of copper in its pathogenesis was established and the autosomal recessive mode of inheritance determined **[5,6].** After the WD-associated gene was localized to chromosome 13, **[7]** it was identified as encoding a metal-transporting P-type adenosine triphosphatase (ATPase). **[8]** This gene, ATPase copper transporting beta (ATP7B), is expressed primarily in hepatocytes. The ATP7B gene product facilitates transmembrane transport of copper into hepatocytes. Absence or impairment of ATP7B function decreases biliary copper excretion, leading to toxic accumulation of hepatocellular copper. The global clinical prevalence of the disease varies by ethnicity, from 12 to 25 cases per million inhabitants. In France, according to an epidemiological study conducted in 2013 by the CRMRWilson, it is 1.5 cases per 100,000 inhabitants. Consanguinity considerably increases its incidence **[1].** As a result, it is quite common in Maghreb countries given the frequency of consanguineous marriages. In Morocco, it remains underestimated due to the difficulty of its diagnosis. In our study, consanguinity was found in 7 patients (53%), all 1st degrees, therefore a family investigation based on the dosage of transaminases, serum ceruloplasmin, cupremia, cupruria was carried out in all our patients, this investigation allowed the diagnosis in 4 cases.

The diagnosis of WD is based on a bundle of clinical, biological and morphological arguments. The Leipzig score is a score that has been proposed by international experts to help the clinician establish a diagnosis of WD from these different items but has not been updated since 2003, not taking into account the new biomarkers currently available **[9].** WD is a clinical chameleon that must be thought of. It usually affects young subjects, classically between 5 and 40 years old, with a peak of revelation during the 2nd and 3rd decades, which is consistent with our series, where the average age of discovery of Wilson's disease was 15.8 years with extremes from 5 to 36 years. However, symptomatic forms of early (2 years) or late (>70 years) revelation have been described. Under these conditions, age in itself does not eliminate a diagnosis of WD**[10].**

Female predominance has been found in the literature: five men for eight women in our series; one man for five women for Ferenci **[11],** six men for ten women for Miranda **[12]** and five men for eight women for Schumacher **[13].**

WD can present with a large number of manifestations, mainly hepatic, neurological and/or psychiatric. In our study, the first manifestations were hepatic in 9 patients (69%). Liver involvement is variable and can manifest as simple abnormalities in liver tests, hepatic steatosis and/or hepatomegaly on imaging, acute or chronic hepatitis, cirrhosis or fulminant hepatitis **[14].** In our series, we had 11 cases of cirrhosis (84%), 6 of which were decompensated and only 1 case of non-serious acute hepatitis. In the series of Walshe and Yealland **[15],** 40% of patients had hepatic dysfunction. In that of Scheinberg and Sterulieb, 44% had liver disease **[16].** In the series of Bonne-Tamir B, 73% of patients had inaugural hepatic manifestations **[17].** Bono w et al, reports liver involvement in 85.7% of cases, whether symptomatic or not **[18].** Neurological involvement may accompany liver involvement or be in the foreground. Dysarthria is the most frequently observed symptom at diagnosis, which may be associated with dystonic involvement, tremor, gait disturbances, parkinsonian syndrome and abnormal choreic movements. Psychiatric manifestations are probably underestimated and are also varied **[14].** Any patient with WD should undergo a thorough neurological examination and in the event of proven neurological involvement, the neurological

assessment should be made using a dedicated scale, called UWDRS (Unified Wilson Disease Rating Scale) **[19],** which has a prognostic interest and will also allow monitoring of the progression of the involvement under treatment. In our series, 4 patients (30%) presented neurological manifestations, including 2 with parkinsonian syndrome, one patient presented with motor slowing and only one patient with a lack of concentration.

The usual ophthalmological manifestations of Wilson's disease are the presence of a Kayser-Fleischer pericorneal green ring. It is carefully sought at the slit lamp by an experienced ophthalmologist and is almost pathognomonic of the disease. But it can be observed in cases of significant cholestasis, particularly in cases of primary or cryptogenic biliary cirrhosis and in cases of primary sclerosing cholangitis **[20,21,22].** There are several observations in the literature of authentic Wilson's disease without a Kayser-Fleischer ring; In our series, it was present in 4 patients (30.7%).

Thrombocytopenia has a dual origin in Wilson's disease, partly due to the excessive destruction of platelets by the spleen in the context of hypersplenism caused by cirrhosis, among other things by the toxic effect of copper on the medullary genesis of platelets (megakaryogenesis) leading to a decrease in their production **[23].** In our series, seven patients had thrombocytopenia.

Other clinical manifestations: Significant extrahepatic manifestations, apart from neurological or psychiatric disease, may be present at the time of diagnosis of W disease **[24].** Gigantism, bluish lunulae, renal abnormalities including aminoaciduria and nephrolithiasis, hypercalciuria and nephrocalcinosis **[25,26],** cardiomyopathy **[27],** myopathy **[28],** chondrocalcinosis and osteoarthritis **[29],** hypoparathyroidism **[30],** pancreatitis **[31],** infertility or repeated miscarriages **[32,33].** No renal, osteoarticular, cardiovascular or endocrine involvement was detected in our series.

Diagnostic methods

Nonspecific laboratory abnormalities: Serum aminotransferase activities are usually abnormal in patients with W disease. The degree of elevation of aminotransferase activity may be relatively mild, disproportionate to the severity of the liver disease. Transient hyperbilirubinemia, mainly unconjugated, may occur during brief episodes of self-limited hemolysis **[34].** In our series, 15.4% of patients had elevated transaminase levels and only 1 patient had total hyperbilirubinemia at 58 mmol/l.

In general, the combination of Kayser-Fleischer rings and a low serum ceruloplasmin level (<0.1 g/L) is sufficient to establish the diagnosis. When Kayser-Fleischer rings are not present, ceruloplasmin levels are not always reliable because they may be low for reasons other than Wilson's disease (e.g., autoimmune hepatitis, severe liver failure in advanced liver disease, celiac disease, familial aceruloplasminemia) or in heterozygous carriers of ATP7B mutations who do not have copper storage disease **[35].** On the other hand, inflammation in the liver or elsewhere may elevate ceruloplasmin concentration to normal levels, reflecting its identity as an acute phase protein. A diagnostic score based on all available tests was proposed by the working group at the 8th International Meeting on Wilson's Disease, Leipzig 2001 **[9].** The Wilson's disease scoring system offers good diagnostic accuracy **[36].**

Ceruloplasmin:

Ceruloplasminemia is decreased in 93% of patients with a threshold of 0.14 g/l for a normal between 0.2 and 0.4 g/l; A normal ceruloplasminemia does not eliminate the diagnosis. Ceruloplasminemia can be increased in cases of inflammation or infection but also in women in cases of estrogen treatment or pregnancy. It can be lowered in heterozygous subjects without developing the disease, but also in cases of liver failure, malabsorption, malnutrition, exudative enteropathy, nephrotic syndrome, acquired copper deficiency, Menkes disease, glycosylation abnormalities and aceruloplasminemia **[1].** In our series, 66% of patients had a lowered ceruloplasmin level.

Serum Copper [1]:

• **Total serum copper assay:** Serum copper is fixed at 92% to ceruloplasmin (holoceruloplasmin). Only the total serum copper assay is available in laboratories. It is generally low (<10 µmol/l or 635 µg/L for a normal between 14 and 21 µmol/l or 890 – 1335 µg/L), but not collapsed due to the increase in the fraction of plasma copper not bound to ceruloplasmin or free copper. In our series, 77% of patients had a low serum copper level.

• **Assay of free copper not bound to ceruloplasmin:** (exchangeable copper and calculation of REC) Serum exchangeable copper (CuEXC) which corresponds to the labile fraction of copper in the serum is, since 2011, a new marker for the diagnosis of WM. It allows to calculate the REC (ratio of exchangeable copper/total serum copper) which is an excellent diagnostic biomarker with a sensitivity and specificity close to 100% for the diagnosis of WM

when its value is > 18.5%. In addition, the REC is of major contribution in family screening, allowing to differentiate heterozygous carriers or healthy subjects from sick subjects when it is > 15%.

Urinary copper [1]:
The 24-hour urinary copper assay is crucial for diagnosis. It reflects the importance of copper overload. The increase in urinary copper is constant in neurological forms, greater than 1.6 µmol or 100 µg per 24 hours (normal less than 0.6 µmol or 40 µg per 24 hours). In certain hepatic or pre-symptomatic forms, copper urine may be normal; a D-penicillamine provocation test is then necessary, but this test is only validated in children. In our series, 77% of patients had a high copper urine rate.

Weight-based assay of intrahepatic copper
Liver biopsy is no longer systematic and should be considered on a case-by-case basis. It then allows the weight-based assay of intrahepatocyte copper, which is indicated in certain hepatic forms, when the copper profile does not confirm the diagnosis. In untreated patients, the threshold of positivity is above 250 µg per gram of dry tissue, but a lower or even normal level does not exclude the diagnosis due to the heterogeneous distribution of intrahepatocyte copper deposits. Cholestatic liver diseases and cirrhosis can cause false positives. Liver histological study can provide diagnostic arguments in favor of the disease and contribute to the evaluation of liver fibrosis **[1].**

Brain MRI:
Magnetic resonance imaging (MRI) of the brain can detect structural abnormalities in the basal ganglia **[37].** The most common finding is a T2 MRI hyperintensity in the basal ganglia region. Abnormal findings are not limited to this region and other abnormalities have been described. A characteristic finding of Wilson disease is the "giant panda face" sign **[38,39],** but is found in only a minority of patients. In addition to this sign, hyperintensities in the tectal plate and central pons, and simultaneous involvement of the basal ganglia, thalamus and brainstem are virtually pathognomonic for Wilson disease [40]. In our series, 50% of patients had NGC involvement on brain MRI.

Treatment [46,47]:
Specific pharmacological treatments:
• **D-penicillamine** is the reference treatment **[1].** It is the most powerful chelator but also potentially the most toxic. It is indicated as a first-line treatment for the treatment of symptomatic forms (hepatic or neurological). The dose administered in adults is 900 to 1800 mg per day in 2 to 3 doses per day. In our series, 84% of patients benefited from treatment based on D penicillamine, with strict and regular monitoring on the clinical level (search for signs of cirrhotic decompensation, neurological and psychiatric signs and skin manifestations), biological by evaluating transaminase levels, TP and copper balance values as well as the performance of inflammatory, renal and blood counts on a regular basis. In our series, no patient presented side effects. The difficulty in our country is to obtain D Penicillamine since this product is not available in Morocco.

• **Trientine**also has chelating properties of free copper by increasing its urinary excretion, coupled with a decrease in the intestinal absorption of copper **[1].** The recommended dose in adults varies from 800 to 1,600 mg/day per day, divided into 2 to 4 doses. It is a second-line treatment used in the event of adverse effects to D-penicillamine or zinc salts, or in the event of therapeutic escape from one of these molecules. This treatment can also be used as a first-line treatment in the event of a contraindication to D-penicillamine.

• **Zinc salt:** Zinc blocks the intestinal absorption of copper. The zinc salt used is zinc acetate (Wilzin® 50 or 25 mg). In adults, the recommended dosage is 150 mg/day in 3 doses **[1].** In our series, 38% of patients benefited from zinc treatment, no patient presented side effects.

Evolution and prognosis:
Untreated Wilson disease is usually fatal, with most patients dying from liver disease and a minority from complications from progressive neurological disease. With chelation therapy and liver transplantation, prolonged survival has become the norm **[41,42].** In general, survival prognosis depends on the severity of liver and neurological disease and compliance with drug therapy. Liver function becomes normal after 1 to 2 years of treatment in most patients without cirrhosis. At the other end of the spectrum, medical therapy is rarely effective in patients with acute liver failure due to Wilson disease, mainly because of the time required to eliminate toxic copper

from the body **[43].** In our series 76% of patients had a good clinical outcome, only 1 patient had epigastralgia and chronic vomiting, and only 1 patient died.

Family screening:
The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend screening first-degree relatives of a patient with Wilson's disease. First-degree relatives include not only siblings, but also offspring and parents of the patient **[44,45].** The interest of the family survey is to allow the treatment of asymptomatic subjects in whom an early diagnosis could be established. In our study, the family survey allowed us to detect 3 cases that were included in the series.

Difficulty of managing Wilson's disease in Morocco: Copper assessment is not a common practice in public hospitals, and its cost is high for a population with limited income. The unavailability of D-penicillamine in the Moroccan market.

Conclusion:-

Wilson's disease is rare and usually manifests itself before the age of 40 by hepatic and/or neuropsychiatric manifestations. However, it should be considered in the event of any unexplained acute or chronic liver abnormality, regardless of the patient's age. Early diagnosis is therefore a key element for a good prognosis of the disease, hence the importance of family screening, which remains the best means of diagnosing asymptomatic forms to this day. Difficulty in managing Wilson's disease in Morocco is linked to several factors, including the unavailability of copper status in public hospitals and the high cost for a population with very limited income; the unavailability of D-penicillamine on the Moroccan market and the lack of an awareness program on the risk of consanguineous marriages.

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